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Orchard On The Trials, Tribulations And Triumphs Of Gene Therapy HTA

by Eliza Slawther

Convincing payers to fund a $3m therapy is no mean feat, even for innovations with curative potential. Orchard Therapeutics, a company with much experience in this field, tells the *Pink Sheet* why it values open dialogues, and outlines how health technology assessment methods could be improved.

Orchard Therapeutics Limited is among the small handful of companies to have a gene therapy approved in the EU. Its ex-vivo autologous hematopoietic stem cell product Libmeldy (atidarsagene autotemcel) was granted an EU marketing authorization in December 2020 for use as a one-time treatment for children with early-onset metachromatic leukodystrophy (MLD), a rare inherited metabolic disease. (Also see "*Advanced Therapies From Orchard & Kite Win EMA Thumbs Up*" - Pink Sheet, 16 Oct, 2020.).

While it is often the regulatory nod that generates buzz for novel therapies, sponsors will know all too well that this is the first of many hurdles on the road to patient access – particularly in the EU, where national health technology assessment (HTA) bodies and payer budgets are highly diverse, according to Orchard's senior vice president of global market access, Francis Pang.

"There's been a big diversity in terms of our experiences with health technology assessment bodies," Pang told the *Pink Sheet* in an interview. He explained that one of the challenges unique to Libmeldy, which corrects the underlying cause of MLD and has a list price of £2.8m ($3.4m) in the UK, was that Orchard had to "educate" some payers and HTA bodies on the *ex vivo* modality of the product.

Ex vivo gene therapies, which involve taking stem cells from the body and modifying them in a lab to replace the faulty gene that causes a certain disease before putting them back into the body, differ significantly from *in vivo* gene therapies, such as Novartis' Zolgensma (onasemnogene abeparvovec), which involve delivering a healthy copy of genes directly into cells

in the body. Both methods use vectors to deliver the therapeutic genetic material, and viral vectors are the most commonly used delivery mechanisms for therapies that are currently available.

Despite the variation in delivery and biological mechanisms of gene therapies on the market today, these advanced therapy medicinal products (ATMPs) often have one thing in common: a high price tag. This has resulted in a tug-of-war between some payers and pharma companies in recent years, although HTA bodies and industry alike have acknowledged that traditional value assessment methods are unsuitable for ATMPs and require a rethink. (Also see "*Dutch HTA Body Hits Out At Bluebird's Zynteglo Pricing*" - Pink Sheet, 29 Jul, 2021.).

Pang, too, suggested that negotiations with HTA bodies have been less of a battle, and more of a joint effort to get Libmeldy to the patients that need it. "The most positive experiences are where you have a very clear and transparent process and the opportunity for dialogue with the particular HTA agency concerned," he said.

Orchard's experience with securing reimbursement for Libmeldy in England is one such example. The country's HTA body, NICE, ensured that the patient perspective was incorporated during its assessment, something Pang stressed is "really important in terms of being able to fill in some of the evidence gaps" that cannot be filled using trial data.

"I think NICE does recognize and give some additional weighting to technologies that have large quality adjusted life years (QALYs)," Pang added, noting that the QALYs gained over a lifetime for a chronic therapy could be around 1.9, compared to more than 20 for a gene therapy.

NICE originally deemed Libmeldy too expensive for use on the National Health Service, but reversed this decision in February 2022 after Orchard agreed to provide the drug at a further confidential discount. (Also see "*Libmeldy: 'Significant Discount' For World's Most Expensive Drug Secures English Funding*" - Pink Sheet, 4 Feb, 2022.)

Libmeldy is also reimbursed, either within its full indication or with limitations, in France, Germany, Italy, the Netherlands and the Nordic countries.

RCTs Unethical

The price tag associated with gene therapies is not the only way in which these products differ from more conventional medicines in the context of HTAs. The trial design, data and post-market evidence generation are also "unique characteristics" that Pang said HTA bodies must recognize.

"In many instances for gene therapies, [evidence is generated] through single-arm clinical studies, for ethical reasons," Pang said. For a fatal disease like MLD with no treatment options

other than the experimental therapy, in this case Libmeldy, denying patients in the control arm the therapy would not be acceptable.

Not only is it unethical to compare a therapy like Libmeldy to placebo in a randomized control trial (RCT), it would also be logistically "really very difficult," to double-blind the study, Pang said, given that patients' own cells have to be removed, genetically modified and reinjected.

While HTA agencies prefer RCT data "for good reason," they are "starting to understand the types of evidence that could be expected with gene therapies," he noted, adding that these organizations are also beginning to develop methods of being able to use these data in their assessments. (Also see "*Gene Therapy HTA: How Do The European, Australian And Canadian Systems Shape Up?*" - Pink Sheet, 25 Sep, 2023.).

Open-Minded Discussions

One of the key value measures that HTA bodies would like to see for a gene therapy would be the durability of its effect over a patient's lifetime. But even for Libmeldy, which has a comparatively lengthy 12 years of follow-up data available, "a bit of extrapolation is required" to determine the value of the product over a lifetime, Pang said.

"From that perspective, it is the understanding or appreciation of the biological mechanism of action which is really important," he said, adding that HTA organizations should also use methods that allow for "flexibility in dealing with uncertainties" and approach negotiations with "open-mindedness."

Similarly, HTA models should be adapted to accommodate data from single-arm studies, for instance through comparison with historical control data or indirect comparisons against other therapies where relevant. "This is possible now, maybe it wasn't 10 years ago, but the statistical methods are available now for that," Pang said.

HTA bodies should also look at the best available data, regardless of whether this has been officially published, Pang said, because it "does take time" for the manuscript process to be completed.

Registries & Real-World Data

The acceptance of data from registries for HTA reassessments is another area that Orchard would like to see developed further, something that is crucial for rare disease therapies.

"You need to have a kind of pan-geographic registry to be able to get a sufficient sample size to inform the statistical inference," Pang explained. Clinical trials are also time-bound by nature, he said, but real-world data gathered from patient registries could provide valuable information about whether the outcomes seen in a trial were achieved in a real-world setting. (Also see "*Gene*

Therapy In The Real World: Long-Term Follow Up Is Key – If Patients Are Willing" - Pink Sheet, 21 May, 2019.).

Although registry data would not be mature enough for use in an initial HTA, it would "certainly be useful for reassessments," Pang noted, adding that HTAs are "'not a once-and-done, as you have reassessments every three to four years."

S2 Scheme 'Laborious'

Although positive reimbursement decisions from national HTA bodies and payers help to facilitate patient access to gene therapies, the complex manufacturing required to deliver these products is yet another challenge that industry and health care authorities must overcome. (Also see "*Gene Therapy's Next Big Challenge: Manufacturing* " - Pink Sheet, 21 Jan, 2019.).

Libmeldy, for instance, must be administered in a qualified treatment center with experience in hematopoietic stem cell transplantation. While Orchard would eventually aim to have a center in each country, the "reality" is that these only exist in a few locations for newly-launched therapies.

Instead, patients can cross borders through a regulatory pathway known as the S2 scheme, an EU law that provides UK, Swiss and EEA citizens with the right to access specialist treatment abroad if it is not available in their home country.

"It's kind of a laborious process, actually – it does take a bit of effort" and "it is not a sustainable pathway," Pang said. For many patients, however, the S2 route is the only way to access novel, advanced treatment options.

The shortcomings of the S2 pathway have been raised as a concern by several industry experts, including the Alliance for Regenerative Medicine, which has called for the establishment of an independent coordination body to oversee requests from patients to use the S2 pathway. (Also see "*ATMPs Put EU Cross-Border Healthcare On The Map*" - Pink Sheet, 19 Feb, 2020.).